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A STUDY ON THE CHLORDIAZEPOXIDE FOR THE TREATMENT OF SPINAL IRRITATION*

by

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INTRODUCTION

JINNAKA (1928), one of the pioneers of orthopaedic surgery in Japan has published that the spinal irritation is one of the symptoms of neurotic diseases such as Beard's disease, hysteria, obsession-neurosis, etc. Based on his report, one of the authors, KONDO (1960) has treated the spinal irritation with a tranquilising drug, meprobamate and has obtained excellent results.

In this paper, the chlordiazepoxide treatment will be published.

CASES

Twenty-five patients suffering from spinal irritation were treated with chlordiazepoxide. They were out-patients of the Orthopaedic Department of the Osaka Medicalal School or the Surgical Department of Naga Public Hospital from the 1st of January, 1962 to 16th of May, 1962.

The twenty-five cases belonged to the third and fifth group of Jinnaka's classification which is shown in Table 1. The age, the sex, and the level of the site were shown in Table 2, 3, and 4.

Table 1. Jinnaka (1928) has classified the pain over the spinous process into five groups as followiog.

1) Pain over the spinous process accompanied by tuberculosis of the spine.
2) Pain over the spinous process accompnied by somatic diseases of the spine other than tuberculosis.
3) spinal irritation.
4) spinous process pain refered from the visceral diseases.
5) constitutional pain.

Table 2. The Age and the Sex.

Age	No. of the cases
0 to 9 years old	
10 to 19 years old	13 cases
20 to 29 years old	10 cases
30 to 39 years old	1 case
40 to 49 years old	
over 50 years old	1 case
total	25 cases

Ratio of the sex (men to women) = 4 : 21

* This paper was read at the 91st meeting of the Kinki Surgical Association, on the 26th of May 1962, at Takatsuki City.

It is reported that some hyperesthesia is considered to be a symptom of the neurotic diseases, when any mechanical changes to cause the hyperesthesia can not be recognized

Table 3. The Level of the Diseased Sites (1)

D. 1.	D. 3.	D. 5. 4 cases	D. 7. 6 cases	D. 9.	D. 11. 1 case
D. 2.	D. 4. 2 cases	D. 6. 9 cases	D. 8. 2 cases	D.10. 1 case	D. 12.
					total 25 cases

Table 4. The Level of the Diseased Site (2)

Case No.	Name	Age	Sex	Level of diseased site	Case No.	Name	Age	Sex	Level of diseased site
1	H. N.	17	female	D. 4	14	T. T.	17	female	D. 6
2	R. K.	22	female	D. 5	15	A. S.	32	female	D. 7
3	O. T.	23	female	D. 7	16	D. G.	18	female	D. 6
4	S. M.	52	male	D. 5	17	S. B.	20	female	D. 5
5	A. R.	19	female	D. 7	18	Y. C.	17	female	D. 6
6	E. J.	23	female	D. 7	19	H. T.	19	male	D. 7
7	T. D.	18	female	D. 4	20	W. S.	25	female	D. 6
8	I. Y.	27	female	D. 6	21	O. E.	18	female	D. 8
9	U. Z.	26	female	D. 6	22	R. G.	16	female	D. 10
10	C. K.	19	female	D. 6	23	D. Y.	19	female	D. 11
11	T. F.	20	female	D. 5	24	M. O.	24	female	D. 6
12	W. N.	19	male	D. 7	25	E. F.	18	female	D. 8
13	E. O.	23	female	D. 6					

in the nerve system. Trausseau has mentioned that the hyperesthesia over the spinous processes is important in the diagnosis of such diseases. Brodie has publiahed that hyperesthesia or hyperalgesia is often found over the spinous process of a neurotic patients. Beujolin, Merlin, Andry, and Charcot have also reported the hyperesthesia and the hyperalgesia to be one of the symptoms of neurotic states.

In the twenty-five patients in this report, nineteen had neurotic complaints ; some had hyperprosexia to the spine, some had anxiety reactions, especially phobia of spine tuberculosis, and some had sleeplessness, agitation, or a history of mental disorders, especially obsession-neurosis.

DOSAGE

The twenty-five cases were out-patients and all of them were treated at the ambulatorium. The dosage was fifteen to thirty miligrams a day, which were divided into three and administered orally after meals. The duration of the administration was three days in the shortest and twenty-nine days in the longest. They are shown in Table 5.

In the chlordiazepoxide treatment, above all in the treatment of the patients with phobia of spine tuberculosis, the authors gave them a persuasive psychotherapy such as explanation of the disease condition, of the hyperprosexia occurrence, and of the tranquilizing function of the drug for the obsession.

The chlordiazepoxide was administered to the patients in which other treatments were not effective, and during the chlordiazepoxide treatment, the other treatments such as drug treatment, physical treatments, etc. were suspended.

RESULTS

The spinal irritation is one of symptoms of neurotic diseases. Accordingly, subjective

Table 5. The Dosage and the Results.

Case No.	Daily Dosage	Duration	Note	Results
1	15emg	10 days	hyperprosexia remarked	remarkable
2	15 mg	7 days	hyperprosexia remarked	poor
3	30 mg	3 days	sleoplessness complained of	remarkable
4	15 mg	5 days	sleeplessness complained of	good
5	30 mg	10 days	phobia of Pott's disease remarked	remarkable
6	30 mg	29 days	phobia of Pott's disease remarked	dramatic
7	15 mg 5 days 30 mg 7 days		phobia of Pott'a disease remarked	dramatic
8	15 mg	5 days	history of hysteria proved	good
9	15 mg	5 days		good
10	15 mg	23 days	sleeplesaness complained of	dramatic
11	30 mg	4 days	sleeplessness complained of	unresponsive
12	15 mg 7 days 30 mg 4 days		sleeplessness complained of	remarkable
13	15 mg 4 days 30 mg 5 days			unresponsive
14	15 mg	10 days	phobia of Pott's diseaee remarked	remarkable
15	15 mg	17 days	phobia of Pott's disease remarked	poor
16	15 mg	3 days		poor
17	15 mg 10 days 30 mg 5 days		sleaplessness complained of	dramatic
18	15 mg	22 days	sleeplessness complained of	dramatic
19	30 mg	3 days	sleeplessness complained of	good
20	15 mg 4 days 30 mg 4 days		phobia of Pott's disease remarked	remarkable
21	20 mg	7 days		good
22	15 mg	10 days		good
23	15 mg 5 days 30 mg 13 days		being complicated by cardioneurosis	good
24	15 mg	5 days		poor
25	15 mg	3 days		remarkable

psychological effects of a drug can not be eliminated and very often the effects become a hindrance to judge the results of the treatment. Still more, in the tranquilizer treatment, the judgement is more difficult. As for the electroencephalogram examination, it is not useful in the judgement of the results, because the neurotic diseases do not have any special patterns of their own. The double blind method by Naruse could not be adopted also, because the patients in this series were too few to get accurate results.

So that the results were mainly judged according to the clinical symptoms and signs as following :

1) The back pain which the patients complained of, and its changes.
2) Tenderness and percussion pain over the spinous process, and their changes.
3) Hyperesthesia or paraesthesia over the spinous process, and their changes.
4) The pateller tendon reflex and Achilles tendon reflex, their acceleration caused by the neurotic conditions, and their changes.
5) The neurotic conditions of the patients, above all hyperprosexia, their changes.

A case in which one symptom or sign of the five disappeared or was much improved was judged (+1); when two of the five symptoms or signs disappeared or much were improved it was judged (+2). In this way, each case was judged (+3), and (+4).

When the five symptoms or signs were much improved, it was judged (+5).

The results of treatment in the cases judged (+1) were described as "poor", (+2) and (+3) were described as "satisfactory", or "good", and (+4) and (+5) were "remarkable". The cases, in which all such complaints, symptoms, and signs disappeared were judged (+6) and were described as "dramatic".

The cases, in which more than two symptoms or signs were moderately improved were also judged (+1) and were described as "poor", when more than four symptoms or signs were moderately improved, the results were judged (+2) and were described as "good".

These results were shown in Table 5, namely "dramatic" in five, "remarkable" in seven, "good" in seven, "poor" in four, and "unresponsive" in two cases.

As for the side effects, three cases complained of sopor. But two of them were a typist and a key-puncher, who were over-worked mentally and manually and had complained of want of sleep before the chlordiazepoxide administration.

It seems interesting too, that the more severe was the neurotic condition, the more effective was the tranquilizing drug ; the results of the meprobamate treatment, which were published in the first report had the same tendency as the chlordiazepoxide treatment. These observations seem to support Jinnaka's report that the spinal irritation is one of the symptoms of the neurotic diseases.

The results of meprobamate treatment are shown in Table 6. and 7.

Table 6. Age, Sex and Level of Site in the Patients suffering from Spinal Irritation, treated with Meprobamcate.

Case No.	Name	Age	Sex	Level of the diseased Site	Case No.	Name	Age	Sex	Level of the diseased Site
1	K. N.	23	female	D. 6	7	N. O.	29	male	D. 10
2	H. H.	30	male	D. 10	8	M. M.	36	female	D. 8
3	C. H.	22	female	D. 5	9	K. K.	26	female	D. 12
4	J. S.	25	male	D. 8	10	Y. N.	16	female	D. 10
5	T. N.	30	male	D, 10	11	H. Y.	18	female	D. 6
6	K. H.	41	female	D. 8	12	J, I.	23	male	D. 5

Table 7. The Dosage and the Results of Meprobamate Treatment for Spinal Irritation.

Case No.	Daily Dosage	Duration	Note	Results
1	1200 mg	4 days	sleeplessness complained of	poor
2	1200 mg	4 days	being complicated by vegetative neurosis	remarkable
3	1200 mg	3 days	hyperprosexia remarked	remarkable
4	1200 mg	9 days	hyperprosexia remarked	dramatic
5	1200 mg	5 days	hyperprosexia remarked	remarkable
6	1200 mg	5 days	hyperprosexia remarked	remarkable
7	1200 mg	3 days		poor
8	1200 mg	9 days		unresponsive
9	1200 mg	4 days		unresponsive
10	1200 mg	7 days		unresponsive
11	1200 mg	2 days	hyperprosexia remarked	dramatic
12	1200 mg	5 days		unresponsive

DISCUSSION

BERGER and BRADLEY (1946) have discovered a new relaxant, myanesin (3-o-toloxyl -1,2,-propanadiol) which is reported by Sakurai to be effective on neurotic diseases.

LUDWIG and PIECH (1950) have synthesized meprobamate (2-methyl-2-n-propyl-1, 3-propanediol dicarbonate), one of the derivatives of myanecin, an excellent tranquilizing action of which has been reported by Berger.

After meprobamate, both the chlorpromazine and reserpine (1952) were introduced to the tranquilizer treatment.

Fig. 1 Myanesine

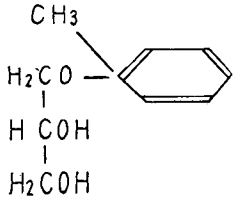


Fig. 2 Meprobamate

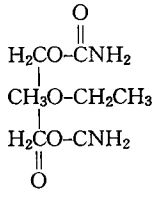
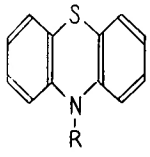


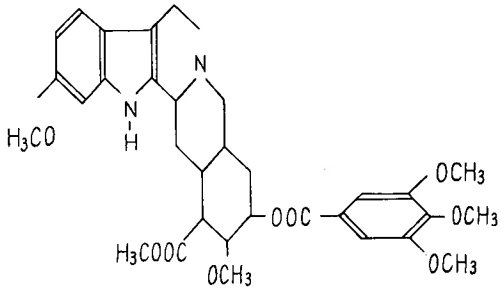
Fig. 3 Derivatives of Phenothiazine



R = -$CH_2CH_2CH_2N(CH_3)_2 \cdot 2Cl$

(*chlorpromazine*)

Fig. 4 Reserpine



The structual formulas of these drugs are shown in Fig. 1, 2, 3, and 4. YAMADA (1958) and OKAMOTO (1958) have each classified the tranquilizers into four groups as following :

1) Phenothiazine group.
2) Resepine group.
3) Diphenylmethane group.
4) Propanediol group.

A representative of the first group is chlorpromazine, a widely known hibernation drug ; in the second group, the most important one is reserpine which is an extract of rauwolfia serpentina and has a depressor action.

The fourth group is derived from myanesin and the most valuable drug of which is meprobamate. It is a characteristic of meprobamate, when compared with the drugs of other groups that the drug has no benzene ring in its structural formula.

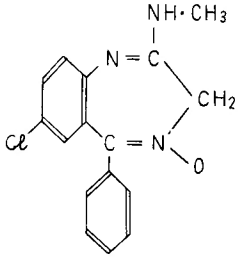
In the third group, some drugs have anti-histamine action, some have anti-convulsant action, and some have anti-hallucinogen action.

The drugs of the first and the second groups are administered in the treatment for severe mental disorders such as manic-depressive psychosis, catatonic syndrome, hallucinosis, etc. The drugs of the third and the fourth groups are administered in the treatment for the neurotic diseases, but Yamada has reported that some drugs of the third group are not suitable for the treatment of the neurotic diseases. Still more, the drugs of the first,

the socond, and the third groups have an action of autonomic block, while neither the meprobamate nor the chlordiazepoxide have such an action.

The chlordiazepoxide is a tranquilizing drug of new type, discovered by STERNBACH (1960) of ROCHE, and the appearance of which is white crystallized powder. The molecular weight is 299.77, the melting point is 238 to 245 degrees C., and not dissolved in water, but dissolved in ether, in aceten or in alcohol. The structural formula (7-chloro-2-methylamino-5-phenyl-3H-1, 4-benzodiazepine-4-oxide) is shown in Fig. 5.

Fig. 5 Chlordiazepoxide



It is reported that the drug has a tranquilizing action of broad spectrum. Lowell has reported an animal experiment with monkeys. He has published that the chlordiazepoxide has some unique tranquilizing actions, when compared with other drugs, that the taming action of the chlordiazepoxide is stronger, while the drug does not restrain the activity of the monkeys (Fig. 6 and Tab. 8).

Table 8 Depressant Effects in Monkeys Minimum Effective Dose (mg/kg)

	Chlordiazepoxide	Meprobamate	Chlorpromazine	Phenobarbital
Behavior, p. o.	1	100	5	20
Ataxia	10	100	5	20
Conditioned avoidance	20	>20	00.24(s.c.)	/

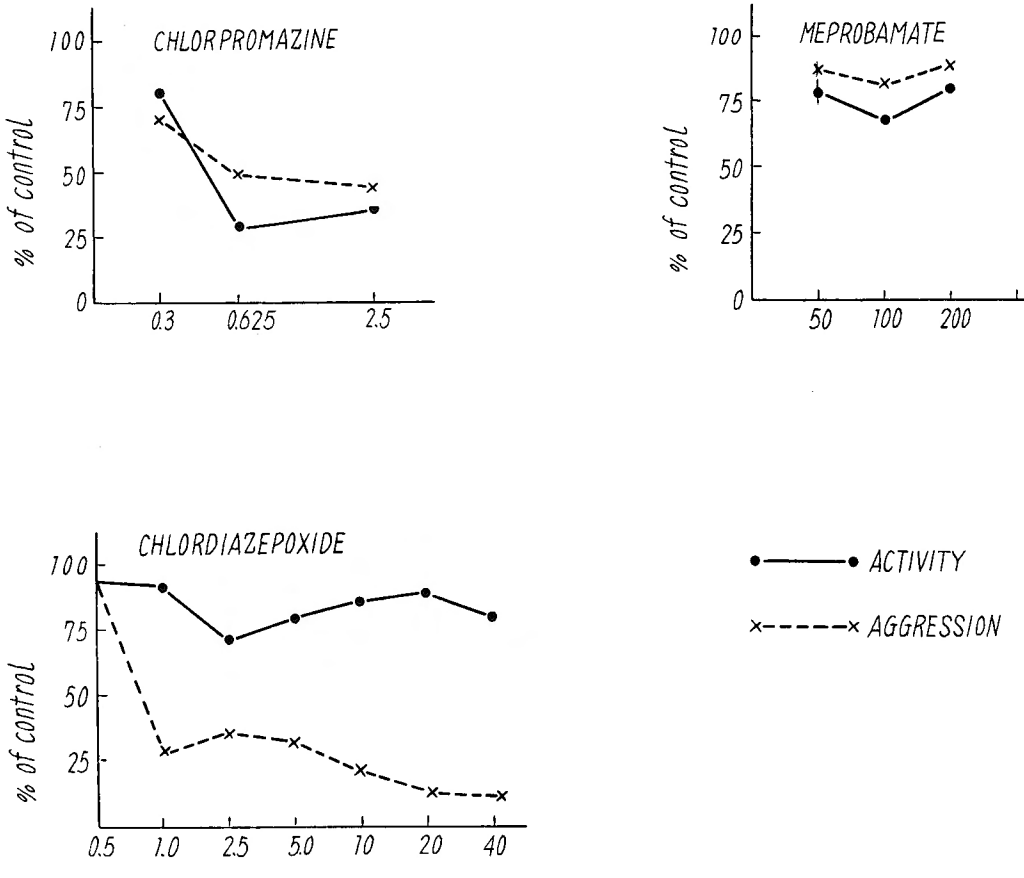
He has also reported another animal experiment with mice to measure the muscle relaxant and anticonvulsant activity of the chlordiazepoxide. From the results of the experiment, he has concluded that the effective anticonvulsant dose of the chlordiazepoxide is nearly the same as meprobamate, but ataxia occures when the effective dose of the meprobamate or the chlorpromazine is adminstered (Fig. 8).

In this series of study on tranquilizer treatment for the spinal irritation, a question has remained, whether the anticonvalsant activity or muscle relaxant activity of the drug has any effects on the results of the treatment or not.

ISHIDA (1957) has published his experiment on the relation between the muscle spasm and the pain. He has injected 6% saline into the m. temporalis and has observed a law of causality in the temporal muscle, in the neck muscle, and in the nape muscle. His observation is that the persisting muscle spasm occures through nociceptive reflex of the deep algesthesia in the muscle, then the second deep algesthesia develops from the muscle spasm, and again the referred pain develops from the spasm.

He has mentioned that vessel stenosis, circulation disturbance, exudation, edema, and nerve stimulation occur in the muscle, as the results of this vicious circle, and that these

Fig. 6 Gross Observations of Aggression and Activity in Monkeys treated with Chlorpromazine, Meprobamate or Chlordiazepoxide.



results and occurance are the same as Zach's spasm-pain-spasm syndrom. He has also described that such persisting muscle spasm is very often occur when the patient is suffering from neurotic diseases, for examples, mental over-work, hyperemotivity, BEARD's disease, etc.

From ISHIDA's observations, both the muscle relaxant activity and the anticonvalsant activity of the drug are useful in the tranquilizer treatment for the spinal irritation.

As for the anticonvulsant action, Keith has reported that metrazol block action of the chlordiazepoxide is stronger than that of meprobamate, chlorpromazine and phenobarbital. He has also published that the electroshock block action of chlordiazepoxide is stronger than that of meprobamate or chlorpromazine, and that the strychinine block action of chlordiazepoxide is stronger than meprobamate (Tab. 9.)

From the results of his experiment with mice, Lowell has mentioned that ptosis caused by the admistration of hypnotics such as phenobarbital, means hypnotic action of the drug, while ptosis caused by the other tranquilizers such as meprobamate or chlorpromazine means autonomic nerve block. The ptosis has not been observed in mice, when chlordiazepoxide is administered (Tab. 9). Still more, chlordiazepoxide has no hypnotic action.

Table 9 Muscle Relaxant and Anticonvulsant Activity in Mice Effective Dose in mg/kg, p.o.

	Chlordiazepoxide	Meprobamate	Chlorpromazine	Phenobarbital
Muscle relaxant	228	256	17	120
Ptosis	0	300	5	120
Hypnotic	0	348	0	122
Metrazol block	18	133	42	33
Electroshock block	95	200	150	20
Strychinine blook	100	500	0	50
Lethal	720	>1000	870	253

These results of Lowell's experiment mean that the drug is suitable for the treatment of outpatients.

The next problem is the toxity of chlordiazepoxide.

As for the acute toxity, the lethal dose (LD 50) is 750 mg/kg. in mice and 2000 mg/kg. in rats, when the drug is administered orally, while the lethal dose of meprobamate is 1600mg/kg. The death is caused by respitatory paralysis.

The chronic toxity has not been noticed in rats both in the physical findings and in the autopsy findings, even the chlordiazepoxide is administered more than one year. Still more, the chlordiazepoxide has appetite stimulating effects and Lowell has reported that the body weight of the experiment animals increased (Tabs. 10. 11).

Table 10. Appetite Stimulating Effects of Chlordiazepoxide

	Dose mg/kg p.o.	% Increase in Food intake
Rat acute	12.5	50
Rat chronic	60	10
Dog acute	1.0	50
Dog chronic	15	26

Table 11

	Chlodiazepoxide	Meprobamate	Chlorpromazine	Phe8obarbital
Taming below staxic case	+	0	0	0
Taming at staxic dose	+	+	+	+
Hypnosis at taming dose	0	+	0	+
Autonomic block	0	0	+	0
Appetite stimulating	+	0	0	0
Muscle relaxation	+	+	+	+
Anticonvulsant	+	+	+	+

On the other hand, James has published the results of chlordiazepoxide treatment for various neurotic diseases. He has mentioned that some neurotic states are difficult to be cured with the chlordiazepoxide only and psychotherapy is required. He has also reported that the psychotherapy itself can be performed more easily when combined with the chlordiazepoxide.

Accodingly, the authors have treated the spinal irritation with the chlordiazepoxide combined with persuative psychotherapy for hyperprosexia, phobia or anxiety reactions, and have got excellent results.

CONCLUSION

From the results of tranquilizer treatment for the spinal irritation, with meprobamate and chlordiazepoxide we have got some conclusions as follows :

1) Tranquilizer treatment for the spinal irritation is successful.

2) The results of tranquilizer treatment seem to support Jinnaka's theory that the spinal irritation is one of the symptoms of the neurotic diseases.
3) Besides the tranquilizig action itself, muscle relaxant activity is useful in the treatment for the back pain of the spinal irritation.
4) The spinal irritation has the same cause as cardioneurosis, gastroneurosis, etc., so that the spinal irritation may safely be called "spinous process neurosis".

SUMMARY

Tranquilizer therapy was tried for the spinal irritation with chlordiazepoxide, because Jinnaka had published a theory that the spinal irritation is one of the symptoms of neurotic diseases.

The results of chlordiazepoxide therapy were excellent and these results seem to support JINNAKA'S theory.

Pharmacology of the chlordiazepoxide was discussed to explain the mechanism of the drug action on the spinal irritation.

Acknowledgement

The authors with to present their acknowledgement to Prof. Yasuji Arihara, whose suggestion and encouragement lead to this work.

The authors are also much thankful to Takada Yakehin Kogyo Co. for giving us the chlordiazepoxide tablets (Contol).

Note

Fig. 6, Tables 8, 9, and 10 were quoted from "Symposium on Newer Antidepressant and Other Psychotherapeutic Drugs (Physicians Post-graduate Press, New York, 1959) by Lowell O.Randall."

Table 11 was quoted from "Pharmacology of Chlordiazepoxide in the Symposium on Chlordiazepoxide (Physicians Postgraduate Press, New York, 1961) by Lowell O. Randall.

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(All of these references have been published in Japanese language.)

和文抄録

脊椎過敏症に対する Chlordiazepoxide 治療に関する研究

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1928年，神中氏はすでに脊椎過敏症は官能性疾患の部分現象と解釈し得る旨を発表している．故に著者は脊椎過敏症に対してトランキライザーの数種の投与を行ない興味ある成績を得た．今回は chlordiazepoxide 製剤であるコントロール使用についての成績を報告する．

患者症例は25例で男性3例，女性22例であり，25例中17例に不眠，注意固着，脊椎カリエスの恐怖，ノイローゼ，ヒステリーの病歴を有していた．

コントール投与量は1日量15mgから30mgに及び，最大投与期間は29日間であつた．

治療効果は全治5例（すべて官能性症状を呈していた）．著効7例，有効7例，やや効4例，無効2例であり，副作用は殆んどみられなかつた．また著者は本症が官能性疾患に基因しているとの神中氏の説を支持するものである．